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Clinical paper

Impaired biological response to aspirin in therapeutic hypothermia comatose patients resuscitated from out-of-hospital cardiac arrest☆

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ABSTRACT

Aim of the study: Acute coronary syndrome is one of the main causes of out-of-hospital cardiac arrest (OHCA). OHCA patients are particularly exposed to high platelet reactivity (HPR) under aspirin (ASA) treatment. The aim was to evaluate HPR-ASA in therapeutic hypothermia comatose patients resuscitated from OHCA.

Methods and results: Twenty-two consecutive patients with OHCA of cardiac origin were prospectively included after therapeutic hypothermia and randomized to receive ASA 100 mg per day, either intravenously ($n = 13$) or orally via a gastric tube ($n = 9$). ADP inhibitors (prasugrel or, if contra-indicated, clopidogrel) were administered in the event of angioplasty. HPR-ASA was assessed by light transmission aggregometry (LTA) with arachidonic acid (AA) and by the PFA-100® system with collagen/epinephrine. Clinical, biological and angiographic characteristics were similar in both groups. Using LTA-AA, maximum aggregation intensity was significantly lower in the intravenous group compared to the oral group (15% vs. 29%, respectively; $p = 0.04$). Overall, 10 patients (45%) had HPR-ASA (38% intravenously vs 56% orally; $p = 0.7$). Similarly, closure time was significantly increased in the IV group (277 s vs. 155 s, respectively; $p = 0.04$).

Conclusion: This study suggests that impaired response to both intravenous and oral aspirin is frequent in comatose patients resuscitated from OHCA.

Introduction

Coronary artery disease (CAD) is documented in approximately two-thirds of patients resuscitated from out-of-hospital cardiac arrest (OHCA) and results in emergency percutaneous coronary intervention for myocardial infarction in one-third with subsequent dual antiplatelet therapy.[1,2]

Antiplatelet therapy is the cornerstone treatment of CAD to prevent atherothrombosis-related events.[3–5] Nevertheless, thrombotic events under treatment reflect potential insufficient response to antiplatelet therapy. Thus, much attention has been directed towards the concept of high platelet reactivity (HPR) under aspirin (ASA) or adenosine diphosphate (ADP) inhibitors.[6,7]

High levels of soluble P-selectin[8] and massive formation of thromboxane A2[9] detected during and after OHCA sustain a hypothesis of platelet and endothelial activation. While the optimal temperature to target during the first hours in patients resuscitated from OHCA remains highly debated,[10] hypothermia is well recognized to affect hemostasis by various complex pathways. It has been shown to result in volume increase and deformation of platelets, to promote platelet margination and to enhance shear-induced

Abbreviations: ADP, adenosine diphosphate; CAD, coronary artery disease; HPR, high platelet reactivity; LTA-AA, light transmission aggregometry with arachidonic acid; LTA-ADP, light transmission agregometry with adenosine diphosphate; MAI, maximum aggregation intensity; OHCA, out-of-hospital cardiac arrest; PFA-Epi, platelet function analyzer-100 with collagen-epinephrin; ROSC, return of spontaneous circulation; ST, stent thrombosis; VASP-PRI, vasodilatator-stimulated phosphoprotein platelet reactivity index.

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platelet aggregation.[11] Taken together, these pathophysiological data highlight a greater risk of HPR under antiplatelet therapy in OHCA patients after therapeutic hypothermia.

In a context of cardiac arrest, most recent studies have focused on the effects of P2Y12 inhibitors on platelet reactivity,[12–14] mainly in therapeutic hypothermia conditions. However, to our best knowledge, no study has evaluated the effects of ASA on platelet aggregation in OHCA patients.

In this study, we evaluated the biological response to ASA, regardless of its route of administration (intravenous or oral) in patients resuscitated from OHCA undergoing coronary angiography and therapeutic mild hypothermia.

Methods

Design

This was a prospective, single-center study conducted in Lariboisiere University Hospital (Paris, France). From January 2013 to December 2014, we included consecutive comatose survivors of OHCA admitted to our medical intensive care unit (ICU). The study was approved by the regional Ethics Committee (IRB 00006477, N° 15-025). Informed consent was obtained from the next of kin and from all survivors.

Patients

Patients were eligible if they were >18 years old, presented return of spontaneous circulation (ROSC) after non-traumatic OHCA of suspected cardiac origin, were comatose (Glasgow coma scale score ≤7) on admission, and required antiplatelet therapy including ASA based on coronary angiography and echocardiography. Exclusion criteria included: pregnancy, refractory cardiac arrest, suspicion of intracranial hemorrhage, known coagulopathy, platelet count outside the 100-500 G/L range, hematocrit <25% and use of GPIIb/IIIa inhibitors within the previous seven days and ASA allergy. Coronary angiography was performed before ICU admission. The treating cardiologist performed stenting according to the international guidelines.[15] After admission, all the patients were treated with therapeutic mild hypothermia using a local standardized protocol. Hypothermia was induced with cold 0.9% saline and maintained using the Arctic Sun® medical temperature management system (Medivence, Colorado, USA) for 24 h at 33 ± 1 °C. Rewarming was then controlled at +0.5 °C/h. All the patients were mechanically ventilated and sedated using midazolam chlorhydrate and sufentanyl citrate. If necessary, atracurium besilate was used to induce neuromuscular blockade to prevent shivering.

Antiplatelet treatment and aggregation tests

After ROSC, the patients received an intravenous loading dose of 250 mg ASA and unfractionated heparin, ranging from 50 to 70 units/kg according to guidelines.[16] After angiography, patients were randomized according to their birth year to receive either intravenous or oral 100 mg ASA daily via a nasogastric feeding tube. When angioplasty was performed, patients received dual antiplatelet therapy. Prasugrel was recommended as first-line treatment with a loading dose of 60 mg. When clopidogrel was used, the loading dose was 600 mg followed by a maintenance dose of 75 mg. The final choice was left to the discretion of the interventional cardiologist between prasugrel or clopidogrel and ground pills were administered via the nasogastric tube. Blood samples were obtained on day 3 in normothermia patients and on day 7 if patients were alive. In the morning, aggregation tests were performed within 30–60 min after blood sampling. Light transmission aggregometry (LTA) with 0.5 mg/mL of arachidonic acid (AA) was performed in our laboratory as previously described.[17,18] HPR was defined by an maximum aggregation intensity (MAI) ≥20% under aspirin treatment (HPR-ASA). HPR-EPI using the PFA-100® system (Dade-Behrin-International, Miami, Florida) was defined by a closure time <193 s with PFA-100 with collagen-epinephrine cartridge (PFA-EPI) under aspirin treatment. LTA triggered by 20 μmol/L adenosine diphosphate (LTA-ADP) was performed and aggregation expressed as the MAI as previously described.[17,18] The PFA-100® with cartridges with membrane coated with type-I collagen and sensitized with 50 μg ADP was also realized. The index of phosphorylation of vasodilatator-stimulated phosphoprotein platelet (VASP-PRI) was determined by whole-blood flow cytometry. HPR-ADP was defined as an MAI >65% using LTA-ADP, closure time <165 s using PFA-ADP and VASP-PRI index >50% by blood flow cytometry.

Statistical analysis

Statistical analysis was performed using IBM-SPSS V.20. The distribution of continuous variables was analyzed using Shapiro–Wilk test. Data with Gaussian distribution were described as mean and standard deviation and analyzed using Student's *t*-tests. Data with non-Gaussian distribution were described as median and interquartiles and analyzed using Mann–Whitney *U* tests. Categorical data were compared using Chi-square tests, except if the absolute number of events in each group was <5, in which case Fischer exact tests were used. *p*-Values below 0.05 were considered as significant.

Results

Patient demographics

Out of a total of 67 screened patients, 22 were prospectively included in this study. The patient flow chart is presented in Fig. 1. All patients received ASA as antiplatelet therapy, intravenously in 13 patients and orally in nine. Thirteen patients received an ADP inhibitor: prasugrel in 10 cases and clopidogrel in three. Baseline characteristics are summarized in Table 1. Cardiovascular risk factors and medications prior to admission were similar in both groups. Coronary angiography was performed in all the patients and percutaneous coronary intervention with stenting achieved in 46% of patients in the IV group versus 66% in the oral group ($p = 0.4$). Anatomical topography of treated vessels was similar in both groups (supplemental data).

Prognostic markers

Ventricular fibrillation was recorded as primary electrocardiogram in 84% of the patients in the IV group versus 66% in the oral group ($p = 0.6$). Location of cardiac arrest, no flow time, time to return of spontaneous circulation and amount of epinephrine administered during cardiopulmonary resuscitation did not differ between the two groups (Table 1). On ICU admission, the mean SOFA score and blood lactate concentrations were not significantly different.

Measurements of platelets reactivity

The main results are summarized in Table 2. MAI was 17.5% [0–64] on day 3 using LTA-AA 0.5 mg/mL. Maximum intensity was significantly lower in the IV group compared to the oral group (15% vs. 29%, $p = 0.04$; Fig. 2). Ten patients (45% of the overall population) developed HPR-ASA (MAI ≥20%) with no significant difference between the groups (38% vs. 56%, $p = 0.7$). Using PFA-EPI, closure time was 250 s [87–300] and significantly more increased in the IV